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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,119	01/12/2001	Sarah S. Bacus	MBHB01-034	1978

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EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/760,119	BACUS, SARAH S.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1,2 and 4-6* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1, 2 and 4-6* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1 and 4-6 have been amended. Claims 1, 2 and 4-6 are pending and under consideration.

Applicant argues that priority should be extended to the 60/176,514 and 60/176, 515 applications in light of the instant amendments to the claims. This has been considered but not found persuasive. The '514 application describes Her2 as a marker; the '515 application describes B-gal and p21 as markers. This fails to provide support for the entirety of the genus of markers on which the instant claims rely, and therefore the effective priority date remains January 12, 2001.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 1 and 4 under 35 U.S.C. 103(a) as being unpatentable over Park et al (Journal of Cancer Research and Clinical Oncology, 2000, Vol. 126, pp. 455-460) in view of Kopp et al (Cancer Research, 1995, Vol.55, pp. 4512-4515) is maintained for reasons of record

Park et al teach that the chemotherapeutic agent, hydroxyurea, induces a senescence-like phenotype in human erythroleukemia cells. Park et al teach the staining of untreated and hydroxyurea treated cells with X-Gal (page 456, line 6 under "SA-B-galactosidase staining"). Park et al teach the induction or increase of p16, p21, and p27 by hydroxyurea using Western blots and anti-p16, anti-p21 and anti-p27 antibodies labeled with a chemiluminescent substrate and detection with an enhanced chemiluminescence detection system (page 456, second column, under "Western blotting analysis", Figure 5 and page 459, lines 23-27) which fulfills the specific limitation of determination of the optical density. Park et al teach that prolonged treatment of the

cells caused cellular senescence as determined by SA Beta galactosidase staining while short term treatment with hydroxyurea caused differentiation (page 458, second column, lines 10-16 under "Discussion"). Park et al suggest the determination of hydroxyurea induced senescence other types of tumor cells and the clinical interest in using hydroxyurea or any other agent which includes senescence in tumor cells for cancer therapy (page 459, last 8 lines). Park et al does not demonstrate the induction or increase of p21, p16 or p27 in a second tumor sample or blood sample taken from a patient after treatment with hydroxyurea or other senescence inducing agent, wherein an increase in p21, p16 or p27 levels is relative to a first tumor sample or blood sample taken from the patient before treatment.

Kopp et al teach the measurement of TGF-Beta2 levels in a patient both before and after chemotherapeutic treatment in order to eliminate the inter-individual differences between patients that would be present if only the post-treatment value was used (page 4512, second column, lines 8-11).

It would have been prima facie obvious at the time the claimed invention was made to assess the increase in levels of p21, p16 or p27 from tumor samples taken from patients or blood samples taken from patients having erythroleukemia as markers of senescence. One of skill in the art would have been motivated to do so by the suggestion of Park et al that hydroxyurea or other cellular senescence inducing agent can be used for a generic cancer therapy. One of skill in the art would have been motivated to use a relative value of increase based on the difference between the post-treatment value and the pre-treatment value in order to overcome individual differences between patients as taught by Kopp et al.

Applicant argues that the combination of references is deficient because Park used only a single cell line which would not provide a nexus to cancer cells in vivo, and because Kopp teaches TGF-beta in plasma rather than in a cell sample. this has been considered but not found persuasive. Park teaches a human erythroleukmia cell line, which would provide a reasonable expectation of success for the same method using human erythroleukemia cells. Further Kopp is relied upon only for the fact that that testing a patient sample both before and after chemotherapy

eliminates inter-individual differences between patients which would be present is only the post-treatment value was used.

The rejection of claims 1, 2, 5 and 6 under 35 U.S.C. 103(a) as being unpatentable over Park et al (Journal of Cancer Research and Clinical Oncology, 2000, Vol. 126, pp. 455-460) and Kopp et al (Cancer Research, 1995, Vol.55, pp. 4512-4515) as applied to claims 1 and 4 above, and further in view of Bentsen et al (U.S. 6,372,895) and Pinkel et al (U.S. 5,665,549) is maintained fro reasons of record.

Claim 5 embodies the method of claim 1 wherein the optical density of the stained cells is performed by image analysis. Claim 6 embodies the method of claim 5 wherein the image analysis is performed by splitting a signal comprising the optical density of the stained cells into a multiplicity of signals that are processed using optical filters having difference absorptions and transmittance properties so that each signal is specific for one of a multiplicity of stains.

The combination of Park et al and Kopp et al render obvious claims 1 and 4 for the reasons set forth above. The combination does not teach image analysis or the specific limitations of claim 6.

Bentsen et al teach an image analysis system comprising emission optical filters, collection optics , focusing optics and an optional light guidance system configures to receive multiple emission signals from each fluorogenic enzyme substrate (column 25, lines 51-67) as well as a beam-splitter (column 26, lines 54-58). Bentsen et al teach the conjugation of fluoresent labels to antibodies (column 21, line 55 to column 22, line 2).

Pinkel et al teach that an image analysis system can be used to enhance or accurately quantitate the intensity differences relative to background staining differences for more accurate and easier result interpretation (column 23, lines 16-20).

It would have been prima facie obvious at the time the claimed invention was made to employ the image analysis system of Bentsen et al for the detection of fluorescently labeled antibodies which bind to p21, p16 and p27. One of skill in the art would have been motivated to do so by the teachings of Bentsen et al regarding the image analysis system for the detection of

fluorescently labeled antibodies and the teachings of Pinkel et al regarding the increased accuracy and ease of interpretation afforded by the use of an image analysis system.

Applicant argues that there is nothing in Bentsen or Pinkel to indicate that they could be used to determine that the systems could be used for determining a response to administration of a cancer chemotherapeutic agent. This has been considered but not fund persuasive. Bentsen and Pinkel would provide a reasonable expectation of success in the determination of an image based on the binding of antibodies. It is expressly noted that Bentsen teaches the detection of a signal in cells or tissues (column 4, lines 5-7) including the detection of galactosidase in animal cells, phosphatases in germ cells, such as bone marrow stromal cells (column 19, lines 22-38). It is concluded that the combination of Bentsen and Pinkle provides a reasonable expectation of success for the detection of the markers rendered obvious by the combination of Park and Kopp.

Claims 1, 2 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Butta et al (Cancer Research, 1992, Vol. 52, pp. 4261-4264) in view of Plant et al (U.S. 5,389,523)

Butta et al teach a method of determining a response to administration of a chemotherapeutic agent, tamoxifen, to human breast cancer in vivo Butta et al teach that immunochemical techniques were used to measure TGF-beta expression in matched breast tumor biopsies taken from patients before and after treatment (page 4261, second column, lines 23-26). Butta et al teach that bound antibodies were localized with the use of biotinylated secondary antibodies (page 4262, first column, lines 23-30). Butta et al do not specifically teach the determination of optical density by ELISA assay. However, it is well known in the art as of the filing date that ELISA is a common immunoassay format and that ELISA plates are read by readers based o optical density measurements as exemplified by Plant et al (column 10, lines 38-39) . It would have been prima facie obvious at the time the claimed invention was made to use an ELISA format to measure the extracellular TGF-beta in the biopsy samples of Butta et al. One of skill in the art would have been motivated to do so because the technology of ELISA is well known.

Claims 1, 2 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Comerci et al (Clinical Cancer Research, 1997, Vol. 3, pp. 157-160) in view of Bacus (U.S. 4,741,043).

Comerci et al teach a method of determining a response to administration of a chemotherapeutic agent, Beta-carotene , to human cervical intraepithelial neoplasia in vivo. Comerci et al teach that matched cervical biopsies taken from 10 patients before and after beta-carotene treatment were stained simultaneously with antibodies to an intracellular and extracellular epitope of TGF-beta (page 158, first column, third full paragraph). Comerci et al teach that bound antibodies were localized with the use of biotinylated secondary antibodies (page 158, first column, second full paragraph). Comerci et al do not specifically teach the determination of optical density by image analysis.

Bacus teaches the determination of optical density by image analysis (column 2, lines 28-29). Bacus teaches that image analysis overcomes staining differences due to batch-to-batch variations in stains (column 2, lines 16-42). Bacus teaches that image analysis is applicable to the analysis of cells as "objects" and in particular to the binding of monoclonal antibodies conjugated to a stain (column 3, lines 42-57).

It would have been prima facie obvious at the time the claimed invention was made to analyze the optical density of biopsy samples of Comercei et al by image analysis. One of skill in the art would have been motivated to do so by the teachings of Bacus on the advantages of image analysis, and also because Comercei et al was using two different antibodies to TGF-beta. One of skill in the art would understand that the image analysis platform.

All claims are rejected.

All other rejections or objections as set forth or maintained in the prior Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A. Canella/
Ph.D., Primary Examiner
Art Unit 1643